REMARKS

Claims 44-55 are active in this application. Claim 44 and 47 are amended for clarity. Support for the amendment to Claim 47 is found on page 4, line 24 to page 5, line 1 of the application. Support for Claim 50-55 is found in Claims 44-49 and the specification as originally filed. No new matter is added by the amendment.

Applicants would like to thank Examiner Hutson for the courtesy of discussing this application with the Applicants undersigned representative on March 6, 2003. The following serves to summarize and expand upon the substance of that discussion.

The primary issue remaining in this application is whether the present claims, i.e., Claims 44-55 are obvious in view of Brisson-Noel et al under the meaning of 35 U.S.C. § 103(a). There is no evidence of record that prior to the present invention that the claimed compositions of proteins were known nor is there evidence that one could, in fact, determine the composition of proteins.

As a basis for maintaining the rejection, the Office has taken the position that one "would have been motivated to sequence the entire isolated 10 kb DNA fragment responsible for vancomycin resistance and identify each open reading frame and express the encoded proteins such that these proteins could be used in determining the mechanism of action in determining vancomycin resistance." (page 5 of the Official Action). Applicants respectfully disagree.

First, the present claims are drawn to a specific combination of proteins such that this composition of proteins confers resistance to glycopeptides in Gram-positive bacteria. Brisson-Noel et al. disclose cloning a 4kb and 6kb Eco R1 fragments of a plasmid, which confers high level glycopeptide resistance in *Enterococcus facium* but does not provide any description as to what those determinants may be and particularly what those sequences would

be. At best, the Brisson-Noel et al publication is an invitation to experiment to try to identify the possible determinants necessary for conferring vancomycin resistance. Brisson-Noel et al does not in any way suggest or provide the requisite expectation that three proteins would be required for the resistance activity.

Furthermore, assuming for arguments sake only that Applicants conceded to the Examiner's rationale that one would have been motivated to sequence and identify the coding regions, the Brisson-Noel et al publication does not, nor could, enable one to sequence the entire sequence of the plasmid to search for the coding regions because the plasmid and the bacteria from which the sequences were originally isolated were NOT in the public's possession. It was not until the filing and publication of the application to which the present application claims priority that the sequences themselves became available to the public.

It is well-established law that in order for a reference to anticipate a claimed invention, the reference or references must provide an enabling disclosure sufficient to place the public in possession of the claimed invention.[1] Likewise, this analysis extends to obviousness, where a holding of obviousness cannot be sustained "unless there is some known or obvious way to make the thing or to carry out the process."[2]

Again, it was not until the filing of the inventor's patent application where the specific nucleotide and amino acid sequences were disclosed, and therefore enabled, that such public availability was provided. Therefore, notwithstanding what the prior art describes, one had no way to sequence the 10 kb Brisson-Noel plasmid because this plasmid was NOT available to the public. As result, one could not identify the coding regions and could not experiment with

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[1]See MPEP 2121.01 and *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

[2]See *In re Collins*, 462 F.2d 538, 174 USPQ 333 (CCPA 1972), citing *In re Hoeksema*, *supra*.

the many possible combinations of proteins to arrive at determining that composition of proteins needed to confer vancomycin resistance.

Thus, a focal issue here becomes whether Brisson-Noel et al enable the claimed invention.

As described in Brisson-Noel et al, the plasmid pIP816 is a natural plasmid isolated from the *E. faecium* strain BM4147 that was vancomycin resistant (see page 924 col. 1, second paragraph and col. 2, second paragraph). The pIP816 plasmid was used to yield various smaller restriction fragments which were cloned into pAT211, pAT212 and pAT213. These plasmids were further characterized and studied in the Brisson-Noel et al publication (see page 924, col. 1 and 2 of Brisson-Noel).

Reference "10" which is cited as the reference for the BM4147 strain in Brisson-Noel et al was the original description of this strain (see page 924, col. 1, third paragraph). Reference "10" is Leclerq et al (1988) "Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*" N Engl J Med 319:157-161. This publication is attached.

As described in Leclerq, the BM4147 strain was isolated in "1986 from the feces of a particular patient with acute leukemia who had not been treated with vancomycin" (see page 157, col. 2, last paragraph) and the plasmid it contained is described in Table 1 on page 158. There is no disclosure that this strain, and therefore the plasmid contained therein, was deposited or accessible to the public in any way.

It is highly improbable that one could successfully isolate the same strain from another patient and in doing so isolate the plasmid with the same sequences as claimed and then identify the sequences necessary to confer vancomycin resistance thereby formulating a composition as in the present claims. In further support of the unique nature of this BM4147 strain and the plasmid it carries, is the disclosure from the attached Leclerq et al publication.

According to Leclerq et al the vancomycin resistant isolates of enterococci (gram-positive bacteria) are rare (page 161, col. 1, last paragraph) and even between the two natural isolates described, there was a high degree of polymorphism with respect to the resistance phenotype (compare the BM4147 and BM4152 clinical isolates in Table 2: "Minimal Inhibitory Concentrations (MIC) of Glycopeptides and Lipopeptide against bacterial strains") as well as the plasmids they carried (see the discussion on page 159, second column, first paragraph: "The patterns generated by *Hind*III (Fig. 1), *Eco*RI, and *Bam*HI (data not shown) for the two plasmids were distinct, although certain fragments had similar electrophoretic properties. Plasmid pIP816 had a size of 34 kb and 10 kb HindIII-generated fragments, whereas pIP817 had a size of 38 kb and 12 fragments.").

This unique nature of biological material is the very reason that the Patent Office imposes a deposit requirement for biological materials on patent applications (see 37 C.F.R. § 1.801-1.809 and MPEP, Chapter 2400): "When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification." (*In re Lundak*, 227 USPQ 90, 93-94 (Fed. Cir. 1985)). See also MPEP § 2402 and *Ajinomoto Co. v Archer Daniels-Midland, Co.*, 56 USPQ2d 1332, 1337-1338: "The deposit of biological organisms for public availability satisfies the enablement requirement for materials that are not amenable to written description or that constitute unique biological materials which can not be duplicated."

Thus, using the Office's own criteria, and applicable law for when biological deposit is required to enable an invention, it is clear that the Brisson-Noel et al do not enable the bacteria or sequences from which one could sequence the entire plasmid insert, identify coding regions, and formulate a composition of coding regions to confer resistance to vancomycin as in the present claims.

Therefore, the present claims would not have been obvious in light of the Brisson-Noel publication and as such withdrawal of the rejection is requested.

In addition, Applicants would like to point out that the Office has already recognized the patentability of the polynucleotides encoding the proteins of SEQ ID NO:2, 4, and 6 in the parent application—see Claim 3 of U.S. patent no. 6,013,508, a copy of which is attached.

The objection to Claim 47 and the rejection of Claims 44-49 under 35 U.S.C. § 112, second paragraph have been addressed by amendment. Applicants thank the Examiner for the helpful suggestions.

Formal drawings are also being filed herewith.

Applicants submit that the present application is now in a condition for allowance. Early notification of such allowance is requested.

Respectfully submitted,

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